

University of Dundee

## Effects of adding Tiotropium or Aclidinium as triple therapy using impulse oscillometry in COPD

Manoharan, Arvind; Morrison, Ashley E.; Lipworth, Brian

*Published in:*  
Lung

*DOI:*  
[10.1007/s00408-015-9839-y](https://doi.org/10.1007/s00408-015-9839-y)

*Publication date:*  
2016

*Licence:*  
CC BY

*Document Version*  
Publisher's PDF, also known as Version of record

[Link to publication in Discovery Research Portal](#)

### *Citation for published version (APA):*

Manoharan, A., Morrison, A. E., & Lipworth, B. (2016). Effects of adding Tiotropium or Aclidinium as triple therapy using impulse oscillometry in COPD. *Lung*, 194(2), 259-266. <https://doi.org/10.1007/s00408-015-9839-y>

### **General rights**

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

### **Take down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

# Effects of Adding Tiotropium or Aclidinium as Triple Therapy Using Impulse Oscillometry in COPD

Arvind Manoharan<sup>1</sup> · Ashley E. Morrison<sup>1</sup> · Brian J. Lipworth<sup>1</sup>

Received: 1 November 2015 / Accepted: 26 December 2015 / Published online: 13 January 2016  
© The Author(s) 2016. This article is published with open access at Springerlink.com

## Abstract

**Introduction** Long-acting muscarinic antagonists confer improvements in spirometry when used in addition to inhaled corticosteroids and long-acting beta-agonists (ICS/LABA) in COPD. The dual objectives of this proof of concept study were to evaluate trough effects of tiotropium (TIO) or aclidinium (ACL) when used as triple therapy and to assess if impulse oscillometry (IOS) might be more sensitive than spirometry in detecting subtle differences in bronchodilator response.

**Methods** Patients with moderate to severe COPD already taking ICS/LABA were randomized to receive add-on therapy in cross-over fashion with either TIO 18 µg od or ACL 322 µg bid for 2–3 weeks each. Measurements of IOS, spirometry, 6-min walk test, St George's Respiratory Questionnaire (SGRQ) and Baseline/Transition Dyspnoea Index (TDI) were made at baseline and after chronic dosing at trough (12 h for ACL and 24 h for TIO), in addition to domiciliary diurnal spirometry.

**Results** 13 patients were completed: mean age 69 years, FEV<sub>1</sub> 52 % predicted, FEV<sub>1</sub>/FVC 0.48, and R5 202 % predicted. There were no differences in any visit-based trough IOS or spirometry outcomes comparing TIO versus ACL. Resonant frequency but not total airway resistance at 5 Hz (R5) significantly improved from baseline with both treatments while peripheral airway resistance (R5–R20) significantly improved with ACL. Visit-based FEV<sub>1</sub>, and forced and relaxed vital capacity were also significantly

improved from baseline with both treatments. There were no significant differences in diurnal FEV<sub>1</sub> and FEV<sub>6</sub> profiles between treatments. 6-min walk distance and post-walk fatigue significantly improved from baseline with ACL, while post-walk dyspnea improved with TIO. SGRQ symptom score significantly improved to a similar degree with both treatments. TDI significantly improved with ACL versus TIO by 1.54 units.

**Conclusion** We observed comparable bronchodilator efficacy at trough with TIO and ACL when used as triple therapy in COPD, while IOS was no more sensitive than spirometry.

**Keywords** COPD · Spirometry · Impulse oscillometry · Tiotropium · Aclidinium

## Introduction

Long-acting muscarinic antagonists (LAMA) are recommended in chronic obstructive pulmonary disease management guidelines [1] as bronchodilator therapy either alone or in combination with long-acting beta-agonists (LABA) and inhaled corticosteroids (ICS). Currently available LAMA include once daily tiotropium (TIO), glycopyrronium (GLYC) and umeclidinium or twice daily aclidinium (ACL). ACL and TIO have similar binding affinities for the M3 receptor and comparable kinetic selectivity for M3 over M2 receptors, while the duration of action for TIO is approximately two-fold longer than that for ACL [2]. For patients with more severe COPD the use of triple therapy with ICS/LABA/LAMA is advocated to improve outcomes including pulmonary function, quality of life, and exacerbations [3–9].

Few studies have however compared different LAMA when used as triple therapy. Once daily use of TIO or

✉ Brian J. Lipworth  
b.j.lipworth@dundee.ac.uk

<sup>1</sup> Scottish Centre for Respiratory Research, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, Scotland, UK

glycopyrronium versus placebo for 12 weeks as add-on therapy to ICS/LABA conferred similar improvements in spirometry and quality of life in patients with moderate to severe COPD [10]. In a chronic dosing comparison of once daily TIO and twice daily ACL as monotherapy for 2 weeks, the diurnal bronchodilator profile showed a noticeable decline in forced expiratory volume in 1 s (FEV<sub>1</sub>) between 12 and 24 h with TIO along with an improvement with ACL after the second evening dose over the same time period, such that the difference was significant [11]. In another study comparing TIO and ACL as monotherapy for 6 weeks, there were similar significant improvements in the 24 h FEV<sub>1</sub> profile with both drugs compared with placebo, while only ACL significantly reduced early morning cough, wheeze, dyspnea, phlegm, and nighttime symptoms versus placebo [12]. In both of these studies [11, 12] there was no significant difference in morning pre dose trough FEV<sub>1</sub> when comparing ACL and TIO after chronic dosing.

Spirometry involves a forced expiratory maneuver which may not be the ideal test to detect subtle improvements in airway caliber in COPD due to effort-dependent small airway closure. Impulse oscillometry (IOS) is an effort-independent test performed during normal quiet breathing, thereby obviating expiratory small airway closure [13]. IOS is easier to perform for patients with COPD during tidal breathing and measures the frequency dependence of airway resistance (R) and reactance (X). As previously described [13], IOS can be used to derive total airway resistance at 5 Hz (R5), central airway resistance at 20 Hz (R20), peripheral resistance (R5–R20), reactance at 5 Hz (X5), and area under the reactance curve (AX) as well as the resonant frequency (RF). In one study using IOS comparing TIO and placebo as add-on to ICS/LABA, there was no significant additive improvement on IOS outcomes with chronic dosing, despite a significant improvement in FEV<sub>1</sub> [9]. However, we are not aware of any studies which have compared different LAMA as triple therapy using IOS.

The dual objectives of this proof of concept study were to evaluate the effects of TIO or ACL at trough when used as add-on therapy to pre-existing ICS/LABA and also to assess whether impulse oscillometry (IOS) might be more sensitive than spirometry in detecting subtle differences in bronchodilator efficacy. We also used domiciliary spirometry measurements to follow diurnal changes in airway caliber at steady state during each randomized treatment period.

## Methods

### Study Participants

Inclusion criteria were male or female volunteers aged 40–80 years with moderate to severe COPD on ICS/

LABA, FEV<sub>1</sub> 30–80 % and smoking history  $\geq 10$  pack-years. Exclusion criteria were other significant respiratory diseases; a COPD exacerbation or respiratory tract infection requiring systemic steroids, and/or antibiotics within 1 month (3 months if hospitalization was required) of the study commencement. The East of Scotland Research Ethics Service granted ethical approval (Ref: 13/ES/0122), and all patients provided written informed consent.

### Study Design

We carried out a randomized, open-label, cross-over study (Fig. 1). Previously prescribed LAMA were stopped at the screening visit. After a 1- to 2-week period on ICS/LABA, patients were randomized to either ACL (Eklira Genuair, Astra Zeneca, Luton, UK) 322 µg bid or TIO (Spiriva HandiHaler, Boehringer, Bracknell, UK) 18 µg bid. Following the run-in period, at visit 1, baseline measurements were recorded. After 2–3 weeks on the study inhaler, participants returned to the department for visit 2. All measurements were taken at trough (i.e., 12 h post dose for ACL and ICS/LABA and 24 h post dose for TIO). Participants attended the department the same time during each study visit. After the first treatment period, participants entered a wash-out period of 1–2 weeks. The same process was repeated with the other study inhaler after cross-over.

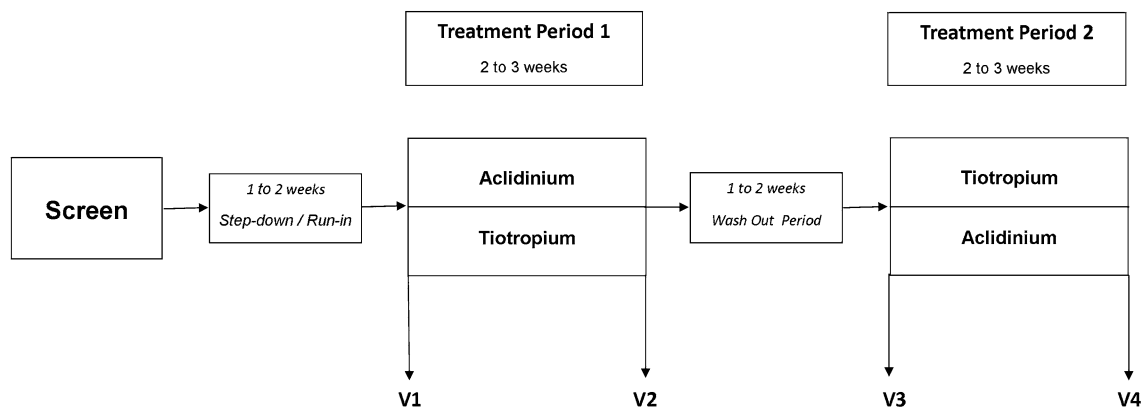
### Primary and Secondary Outcomes

The primary outcome was change in trough R5 from baseline after chronic dosing. Secondary outcomes included change from baseline in the remaining IOS variables

(R20, R5–R20, X5, RF and AX), spirometry including FEV<sub>1</sub>, forced mid-expiratory flow between 25 and 75 % of forced vital capacity (FEF<sub>25–75</sub>), forced vital capacity (FVC), relaxed vital capacity (RVC), 6-min walk test (6MWT), domiciliary PiKo-6 measurements for FEV<sub>1</sub> and FEV<sub>6</sub>, St George's Respiratory Questionnaire (SGRQ) and Baseline/Transition Dyspnoea Index (BDI-TDI).

### Measurements

Impulse oscillometry (Masterscreen IOS, Höchberg, Germany) was performed in triplicate according to the manufacturer's instructions. Spirometry was performed using a SuperSpiro (Micro Medical Ltd, Chatham, Kent, UK). Domiciliary FEV<sub>1</sub> & FEV<sub>6</sub> measurements were recorded using a handheld PiKo-6 monitor (n-Spire Health, Longmont, CO, USA). Domiciliary PiKo-6 measurements were recorded at trough for both drugs; and after each morning and evening dose of ACL (i.e., 2 h post dose); or at corresponding times after each morning dose of TIO (i.e., 2 and 14 h post dose).



**Fig. 1** After a 1- to 2-week run-in, patients received either tiotropium 18 µg od or aclidinium 322 µg bid for 2–3 weeks each with a 1- to 2-week wash-out in between. Baseline values were measured at Visit 1/3 and after chronic dosing at Visit 2/4

### Statistical Analysis

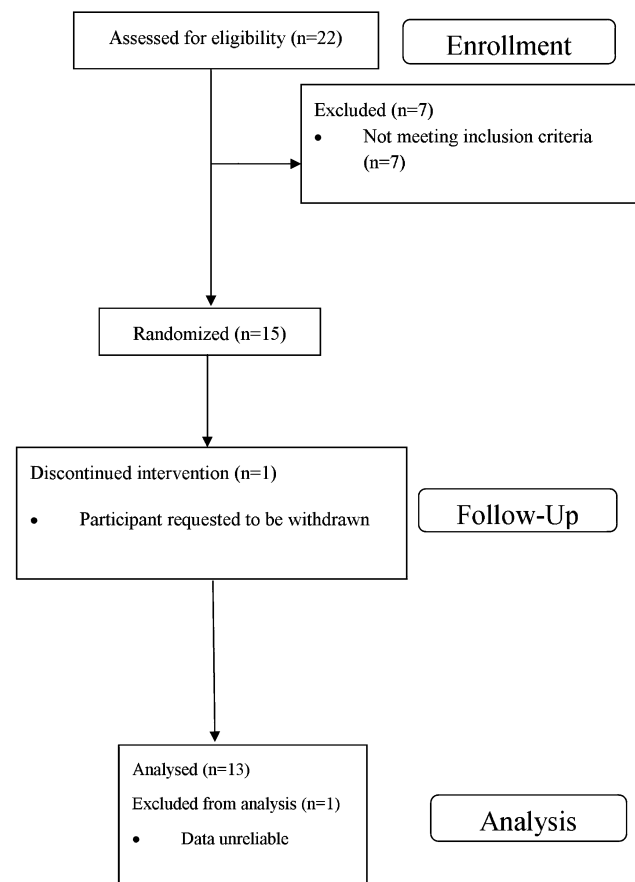
The study was powered at 80 % to detect a  $0.1 \text{ kPa L}^{-1} \text{ s}$  difference in the primary outcome of trough R5, assuming a within subject standard deviation of  $0.13 \text{ kPa L}^{-1} \text{ s}$ , and an alpha error of 0.05 (two-tailed). Data were first examined for normality of distribution. Paired Students *t*-tests were used to compare between treatment effects at either baseline and after each chronic dosing, as well as within treatment effects comparing baseline versus chronic dosing. Repeated measures analysis of variance was used to assess the diurnal profile from serial domiciliary FEV<sub>1</sub> and FEV<sub>6</sub> measurements using the average from the last week of each randomized treatment period and the last week of each baseline.

### Results

Thirteen patients were completed per protocol (Fig. 2): age 69 years, 10 males, and mean of 47 pack-years. Post-bronchodilator FEV<sub>1</sub> was 52 % predicted with 10 % reversibility, FEV<sub>1</sub>/FVC ratio was 0.48, and R5 % was 202 % predicted. Nine patients were taking fluticasone/salmeterol, 3 budesonide/formoterol, and 1 beclomethasone/formoterol, with a mean beclomethasone equivalent dose of  $1000 \mu\text{g day}^{-1}$ . 11 patients were taking LAMA: 8 with TIO, 2 with ACL, and 1 with glycopyrronium.

Baseline values prior to randomized treatments were not significantly different, and there were also no significant differences in baselines according to visit sequence. There were no differences in any visit-based trough IOS or spirometry outcomes comparing TIO versus ACL (Table 1; Fig. 3). Resonant frequency (RF) but not total airway resistance at 5 Hz (R5) significantly improved from baseline within both treatments, while peripheral airway resistance (R5–R20) significantly improved with ACL

### CONSORT Flow Diagram



**Fig. 2** CONSORT diagram showing the flow of participants through the study

(Tables 2, 3). Visit-based FEV<sub>1</sub>, FVC, and RVC were also significantly improved from baseline within both treatments (Tables 2, 3). There were no significant differences between treatments at any time points during the diurnal FEV<sub>1</sub> and FEV<sub>6</sub> profiles (Fig. 4).

There were no significant differences between treatments for the 6-min walk test (Table 1). Six-min walk distance and post-walk fatigue significantly improved from baseline with ACL, while post-walk dyspnea improved with TIO (Tables 2, 3). Post-walk heart rate and oxygen saturation were not significantly altered by either treatment (Fig. 5).

SGRQ symptom score significantly improved with both drugs from baseline, but there was no difference between treatments total or symptoms score (Tables 1, 2, 3). Mean BDI was 6.54, while TDI was significantly improved by ACL (1.0) versus TIO (−0.54): mean difference 1.54 (95 % CI 0.39–2.69),  $P = 0.013$ .

## Discussion

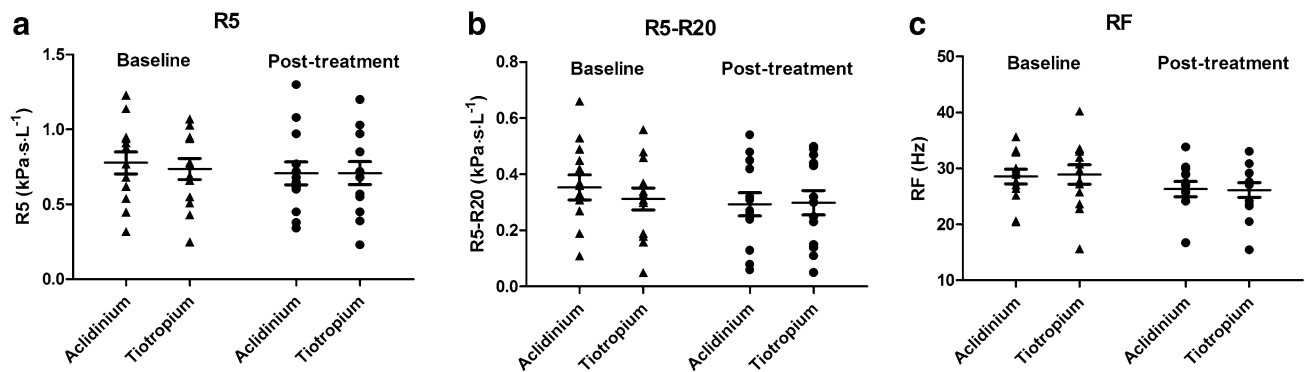
The results of this proof of concept study showed no significant differences between randomized treatments in any IOS or spirometry outcomes measured at trough after chronic dosing with TIO and ACL when used as triple therapy in patients with COPD. We found no significant difference between treatments in the primary outcome of

R5, although neither drug produced any significant improvements in R5 from baseline. Within the power constraints of the sample size, we cannot exclude the possibility that we may have missed a difference in R5 smaller than  $0.1 \text{ kPa L}^{-1} \text{ s}$ , which we considered to be a clinically important difference. Other IOS outcomes including R20, X5, and AX were not significantly improved from baseline with either drug from baseline. Nonetheless, we showed that both treatments produced comparable significant improvements from baseline in RF, while ACL also produced a significant improvement in R5–R20. However, the clinical relevance of small changes in IOS outcomes in COPD is uncertain as there are currently no published data with regard to minimal important differences. In one cross-sectional study in COPD patients, peripheral airway resistance correlated with  $FEV_1$  and  $FEF_{25-75}$  but not with the Medical Research Council (MRC) dyspnea score [14]. In a baseline cross-sectional analysis of the ECLIPSE study in COPD, IOS was found to be reproducible and was able to define the severity of disease according to global initiative for chronic obstructive lung disease (GOLD) status [15].

**Table 1** Change from baseline for acclidinium versus tiotropium

Parameter	Acclidinium	Tiotropium	Difference (95 % CI)	<i>P</i> value
$FEV_1$ (L)	0.11	0.15	−0.04 (−0.13, 0.05)	0.36
FVC (L)	0.28	0.24	0.03 (−0.16, 0.23)	0.72
$FEF_{25-75}$ (L s <sup>−1</sup> )	0.02	0.06	−0.04 (−0.10, 0.01)	0.13
RVC (L)	0.30	0.22	0.08 (−0.12, 0.28)	0.39
RVC/FVC	0.01	−0.05	0.06 (−0.09, 0.21)	0.38
R5 (kPa L <sup>−1</sup> s)	−0.07	−0.03	−0.04 (−0.12, 0.04)	0.29
R20 (kPa L <sup>−1</sup> s)	−0.01	−0.02	0.01 (−0.05, 0.06)	0.80
R5–R20 (kPa L <sup>−1</sup> s)	−0.06	−0.01	−0.05 (−0.11, 0.02)	0.13
X5 (kPa L <sup>−1</sup> s)	0.03	0.05	−0.02 (−0.09, 0.06)	0.62
RF (Hz)	−2.22	−2.77	0.54 (−2.90, 3.99)	0.74
AX (kPa L <sup>−1</sup> )	−0.70	−0.55	−0.15 (−0.84, 0.54)	0.65
6MWT				
Distance (m)	36	9	27 (−2, 56)	0.07
Post-walk oxygen saturation (%)	0	0	0 (−2, 2)	0.93
Post-walk heart rate (bpm)	3	1	2 (−2, 6)	0.36
Post-walk dyspnoea (Borg scale)	−0.6	−0.7	0.1 (−0.6, 0.7)	0.79
Post-walk fatigue (Borg scale)	−0.5	−0.3	−0.2 (−0.6, 0.2)	0.34
SGRQ				
Symptoms score	−7.35	−7.31	−0.03 (−5.66, 5.59)	0.99
Total score	−0.97	−2.35	1.38 (−1.85, 4.61)	0.37

Mean values for change from baseline are shown each drug as well as the difference between the drugs  $FEV_1$  forced expiratory volume in 1 s,  $FVC$  forced vital capacity,  $FEF_{25-75}$  forced mid-expiratory flow between 25 and 75 % of forced vital capacity,  $RVC$  relaxed vital capacity,  $R5$  total airway resistance at 5 Hz,  $R20$  central airway resistance at 20 Hz,  $R5-R20$  peripheral airway resistance as the difference between 5 Hz and 20 Hz,  $RF$  resonant frequency,  $X5$  reactance at 5 Hz,  $AX$  reactance area,  $6MWT$  6-min walk test, bpm beats per minute,  $SGRQ$  St George's Respiratory Questionnaire



**Fig. 3** Effects on impulse oscillometry outcomes at baseline and post-treatment with either tiotropium or acclidinium. Data are depicted for individuals as well as means and SEM. **a** R5 total airway resistance **b** R5–R20 peripheral airway resistance **c** RF resonant

frequency. There were significant improvements from baseline in RF with acclidinium ( $P < 0.05$ ) and tiotropium ( $P < 0.01$ ), and in R5–20 with tiotropium ( $P < 0.05$ ). There were no significant differences between tiotropium and acclidinium in any oscillometry outcomes

**Table 2** Within acclidinium: baseline versus post-treatment

Parameter	Baseline	Post-acclidinium	Difference (95 % CI)	<i>P</i> value
FEV <sub>1</sub> (L)	1.21	1.32	0.11 (0.03, 0.18)	0.009
FVC (L)	2.67	2.95	0.28 (0.05, 0.50)	0.02
FEF <sub>25–75</sub> (L s <sup>-1</sup> )	0.46	0.48	0.02 (−0.04, 0.08)	0.50
RVC (L)	3.12	3.43	0.30 (0.19, 0.42)	<0.0001
RVC/FVC	1.17	1.18	0.01 (−0.08, 0.10)	0.76
R5 (kPa L <sup>-1</sup> s)	0.78	0.71	−0.07 (−0.15, 0.01)	0.07
R20 (kPa L <sup>-1</sup> s)	0.42	0.41	−0.01 (−0.04, 0.03)	0.61
R5–R20 (kPa L <sup>-1</sup> s)	0.35	0.29	−0.06 (−0.11, −0.01)	0.02
X5 (kPa L <sup>-1</sup> s)	−0.38	−0.34	0.03 (−0.04, 0.11)	0.36
RF (Hz)	28.54	26.32	−2.22 (−4.37, −0.08)	0.04
AX (kPa L <sup>-1</sup> )	4.29	3.58	−0.71 (−1.49, 0.07)	0.07
6MWT				
Distance (m)	406	442	36 (1, 70)	0.045
Post-walk oxygen saturation (%)	91	92	0 (−2, 2)	0.73
Post-walk heart rate (bpm)	76	79	3 (0, 6)	0.08
Post-walk dyspnoea (Borg scale)	2.7	2.2	−0.6 (−1.2, 0.1)	0.08
Post-walk fatigue (Borg scale)	2.2	1.7	−0.5 (−1.0, 0.0)	0.04
SGRQ				
Symptoms score	45.10	37.76	−7.35 (−14.12, −0.57)	0.04
Total score	36.75	35.78	−0.97 (−4.51, 2.57)	0.56

Mean values are shown

FEV<sub>1</sub> forced expiratory volume in 1 s, FVC forced vital capacity, FEF<sub>25–75</sub> forced mid-expiratory flow between 25 and 75 % of forced vital capacity, RVC relaxed vital capacity, R5 total airway resistance at 5 Hz, R20 central airway resistance at 20 Hz, R5–R20 peripheral airway resistance as the difference between 5 Hz and 20 Hz, RF resonant frequency, X5 reactance at 5 Hz, AX reactance area, 6MWT 6-min walk test, bpm beats per minute, SGRQ St George's Respiratory Questionnaire

We are aware of only one other clinical trial evaluating triple therapy in COPD using IOS. In that study, Williamson et al. enrolled patients with severe COPD (FEV<sub>1</sub> 42 %) comparing 2 weeks of TIO and placebo as add-on to ICS/LABA [9]. IOS outcomes including R5, R20, and X5 were not significantly different after 2 weeks of treatment

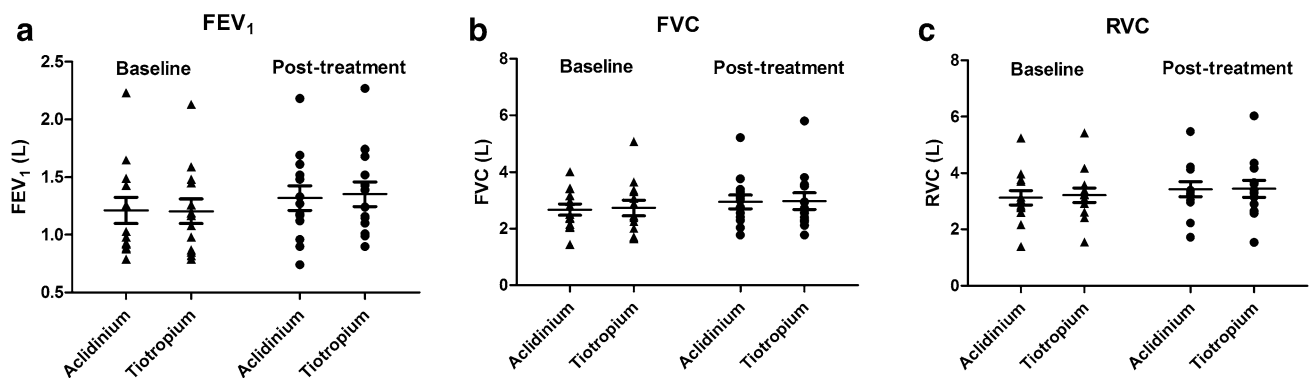
despite a significant improvement in FEV<sub>1</sub>. This disconnect between improvements in FEV<sub>1</sub> but not R5 in response to TIO after 2 weeks is consistent with our current findings. Moreover, the mean R5 at baseline on ICS/LABA prior to TIO reported by Williamson et al. was 0.7 kPa L<sup>-1</sup> s which is similar to baseline R5 values in our patients.

**Table 3** Within tiotropium: baseline versus post-treatment

Parameter	Baseline	Post-tiotropium	Difference (95 % CI)	<i>P</i> value
FEV <sub>1</sub> (L)	1.20	1.35	0.15 (0.10, 0.20)	<0.0001
FVC (L)	2.73	2.97	0.24 (0.10, 0.39)	0.003
FEF <sub>25–75</sub> (L s <sup>-1</sup> )	0.47	0.53	0.06 (0.02, 0.10)	0.004
RVC (L)	3.22	3.44	0.22 (0.04, 0.41)	0.02
RVC/FVC	1.23	1.18	−0.05 (−0.16, 0.06)	0.32
R5 (kPa L <sup>-1</sup> s)	0.74	0.71	−0.03 (−0.09, 0.03)	0.30
R20 (kPa L <sup>-1</sup> s)	0.42	0.41	−0.01 (−0.04, 0.02)	0.36
R5–R20 (kPa L <sup>-1</sup> s)	0.31	0.30	−0.01 (−0.07, 0.04)	0.58
X5 (kPa L <sup>-1</sup> s)	−0.37	−0.33	0.05 (−0.01, 0.11)	0.12
RF (Hz)	28.90	26.13	−2.77 (−4.58, −0.96)	0.006
AX (kPa L <sup>-1</sup> )	4.21	3.66	−0.55 (−1.16, 0.05)	0.07
6MWT				
Distance (m)	429	437	9 (−13, 30)	0.40
Post-walk oxygen saturation (%)	92	93	0 (−1, 2)	0.64
Post-walk heart rate (bpm)	75	76	1 (−2, 4)	0.49
Post-walk dyspnoea (Borg scale)	2.8	2.1	−0.7 (−1.2, −0.1)	0.03
Post-walk fatigue (Borg scale)	2.4	2.1	−0.3 (−0.8, 0.2)	0.21
SGRQ				
Symptoms score	47.34	40.03	−7.31 (−14.62, 0.00)	0.05
Total score	38.85	36.50	−2.35 (−5.71, 1.02)	0.15

Mean values are shown

FEV<sub>1</sub> forced expiratory volume in 1 s, FVC forced vital capacity, FEF<sub>25–75</sub> forced mid-expiratory flow between 25 and 75 % of forced vital capacity, RVC relaxed vital capacity, R5 total airway resistance at 5 Hz, R20 central airway resistance at 20 Hz, R5–R20 peripheral airway resistance as the difference between 5 Hz and 20 Hz, RF resonant frequency, X5 reactance at 5 Hz, AX reactance area, 6MWT 6-min walk test, bpm beats per minute, SGRQ St George's Respiratory Questionnaire



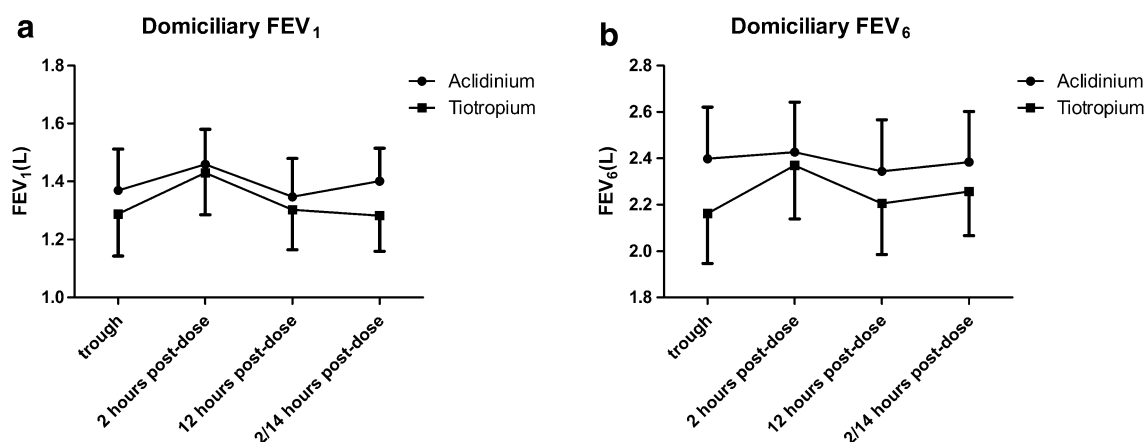
**Fig. 4** Effects on spirometry outcomes at baseline and post-treatment with either tiotropium or acclidinium. Data are depicted for individuals as well as means and SEM. **a** FEV<sub>1</sub> forced expiratory volume in 1 s **b** FVC forced vital capacity **c** RVC relaxed vital capacity. There were significant improvements from baseline for FEV<sub>1</sub> within acclidinium

( $P < 0.01$ ) and tiotropium ( $P < 0.0001$ ), for FVC within acclidinium ( $P < 0.05$ ) and tiotropium ( $P < 0.01$ ), and for RVC within acclidinium ( $P < 0.0001$ ) and tiotropium ( $P < 0.05$ ). There were no significant differences between tiotropium and acclidinium in any spirometry outcomes

Perhaps performing a further evaluation using a full 24-h profile with serial IOS as an area under the curve (AUC) might be able to detect more subtle differences in airway caliber which we did not observe on a single trough measurement.

Whole-body plethysmography is alternative effort-independent test using a panting maneuver which can measure airway resistance (or its reciprocal as conductance) but is more difficult and time consuming to perform than IOS. Singh et al. reported on a comparison of fluticasone/





**Fig. 5** Diurnal profiles with either tiotropium given once daily in the morning or acclidinium given twice daily in the morning and evening, for the last week of each randomized treatment. Data are depicted as means and SEM. **a** FEV<sub>1</sub> forced expiratory volume in 1 s **b** FEV<sub>6</sub> forced expiratory volume in 6 s. Data are shown for the morning

trough measurement (i.e., pre-dose for acclidinium and tiotropium), 2 and 12 h post dose (i.e., trough for acclidinium), and 2 h post the evening dose of acclidinium or 14 h after the morning dose of tiotropium. There were no significant differences between tiotropium and acclidinium at any time points

salmeterol versus fluticasone/salmeterol/TIO for 2 weeks in patients with COPD, where the primary outcome of peak specific airway conductance (as AUC 0–4 h) showed a 27 % significant difference in favor of triple therapy, while for trough FEV<sub>1</sub>, there was a significant mean difference of 110 ml [3]. In our study, we showed significant within treatment improvements in mean trough FEV<sub>1</sub> amounting to 110 ml with ACL and 150 ml with TIO, as compared to the minimal important difference of 100–140 ml [16].

For visit-based spirometry outcomes including FEV<sub>1</sub>, FVC, and RVC we observed significant within treatment effects compared to baseline in response to TIO and ACL, but no difference between treatments. Moreover, there were no significant differences between treatments for domiciliary diurnal profiles of FEV<sub>1</sub> and FEV<sub>6</sub>. In a previous comparison of the same doses of TIO and ACL used as monotherapy, there were no differences between drugs in terms of trough pre-dose FEV<sub>1</sub> measurements after 2 weeks, although the AUC 12–24 h for the visit-based diurnal FEV<sub>1</sub> profile was significantly better with ACL compared to TIO after chronic dosing [11]. This observed difference in the FEV<sub>1</sub> AUC 12–24 h corresponds to the 12-h period after taking the evening dose of ACL when the effect of TIO is beginning to wane throughout the night time prior to the next morning dose. Perhaps on reflection, we might have also shown such differences in domiciliary FEV<sub>1</sub> if we had performed diurnal evening measurements between the 14- and 24-h time point for TIO, although we considered that this was not practical for elderly patients to perform at home. Another possibility is that in the present study, there may be less room for further improvement conferred by LAMA when given as add-on to ICS/LABA compared to its use as monotherapy. In a previous comparison of TIO and GLYC as add-on to ICS/LABA, the

mean difference in the primary outcome of trough FEV<sub>1</sub> amounted to 7 ml [10], as compared to a 40 ml difference between TIO and ACL in the present study.

We used dry powder formulations of TIO and ACL which emit coarse particles >2 µm, which could also explain the somewhat limited improvements in pulmonary function. In this regard, we are not aware of any head to head lung deposition studies comparing TIO and ACL dry powder formulations in COPD. Perhaps using smaller particle formulations such as the fine-mist TIO Respimat inhaler might result in greater improvements in regional lung deposition.

With the development of single inhaler triple therapy, it will be important to know what the impact is on more clinically relevant outcomes. In a retrospective cohort study of 2853 patients with moderate to severe COPD followed up over 4.65 years, there were 996 receiving ICS/LABA (FEV<sub>1</sub> of 63 %) and 1857 receiving ICS/LABA/LAMA (FEV<sub>1</sub> of 51 %) [17]. Comparing triple versus dual therapy, there was a 15 % reduction in hospital admissions, 29 % fewer oral corticosteroid bursts, and 26 % lower all-cause mortality, while triple therapy was associated with a fall in serial FEV<sub>1</sub> of 30 ml over 4 years.

Aside from pulmonary function outcomes, it is also important to consider the impact of treatment upon functional status (6-min walk distance and dyspnoea index) and health-related quality of life (SGRQ) [16]. While we observed no difference between treatments in 6-min walking distance, there was a 36 m mean improvement from baseline with ACL, which exceeds the minimal important difference of 25 m [18, 19]. There was a significant improvement post-walk fatigue with ACL and in post-walk dyspnoea with TIO, but no differences were seen in either outcome between treatments. Furthermore post-



walk heart rate and oxygen saturation did not change with either treatment. In terms of quality of life, although the SGRQ symptoms score was significantly improved with both drugs, there was no difference between them. The transition dyspnoea index was significantly improved by ACL versus TIO by a mean difference of 1.54 which exceeded the minimal important difference of 1.0 [20]. The relevance of this finding in the absence of any differences in objective pulmonary function outcomes is uncertain.

In summary, we observed comparable bronchodilator efficacy at trough with TIO and ACL when used as triple therapy in COPD, while IOS was no more sensitive than spirometry. The utility of IOS measurements in COPD requires further evaluation perhaps using a diurnal IOS profile to compare with spirometry or whole-body plethysmography.

**Acknowledgments** We would like to thank Almirall for the unrestricted grant and supply of the ACL inhalers.

**Funding** This study was funded by an unrestricted grant from Almirall. Almirall did not have any role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

#### Compliance with Ethical Standards

**Conflicts of interest** The Scottish Centre for Respiratory Research has received an unrestricted Grant from Almirall to support the present study and from AstraZeneca for recruiting into a multicentre trial. BJL has received payments from Boehringer for consulting and attending advisory boards as well as support for attending the British Thoracic Society and European Respiratory Society and American Academy of Allergy Asthma and Immunology. AM and AEM have no conflicts of interest to declare.

**Ethical Standards** This manuscript complies with the current laws of the United Kingdom

**Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

## References

- Vestbo J, Hurd SS, Agusti AG et al (2013) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 187(4):347–365
- Gavalda A, Ramos I, Carcasona C et al (2014) The in vitro and in vivo profile of aclidinium bromide in comparison with glycopyrronium bromide. *Pulm Pharmacol Ther* 28(2):114–121
- Singh D, Brooks J, Hagan G, Cahn A, O'Connor BJ (2008) Superiority of “triple” therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. *Thorax* 63(7):592–598
- Hanania NA, Crater GD, Morris AN, Emmett AH, O'Dell DM, Niewoehner DE (2012) Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. *Respir Med* 106(1):91–101
- Jung KS, Park HY, Park SY et al (2012) Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: a randomized controlled study. *Respir Med* 106(3):382–389
- Welte T, Miravittles M, Hernandez P et al (2009) Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 180(8):741–750
- Aaron SD, Vandemheen KL, Fergusson D et al (2007) Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 146(8):545–555
- Cazzola M, Ando F, Santus P et al (2007) A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. *Pulm Pharmacol Ther* 20(5):556–561
- Williamson PA, Short PM, Clearie KL et al (2010) Paradoxical trough effects of triple therapy with budesonide/formoterol and tiotropium bromide on pulmonary function outcomes in COPD. *Chest* 138(3):595–604
- Frith PA, Thompson PJ, Ratnavadivel R et al (2015) Glycopyrronium once-daily significantly improves lung function and health status when combined with salmeterol/fluticasone in patients with COPD: the GLISTEN study—a randomised controlled trial. *Thorax* 70(6):519–527
- Fuhr R, Magnussen H, Sarem K et al (2012) Efficacy of aclidinium bromide 400 µg twice daily compared with placebo and tiotropium in patients with moderate to severe COPD. *Chest* 141(3):745–752
- Beier J, Kirsten AM, Mroz R et al (2013) Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: results from a 6-week, randomized, controlled Phase IIIb study. *COPD* 10(4):511–522
- Williamson PA, Clearie K, Menzies D, Vaidyanathan S, Lipworth BJ (2011) Assessment of small-airways disease using alveolar nitric oxide and impulse oscillometry in asthma and COPD. *Lung* 189(2):121–129
- Anderson WJ, Lipworth BJ (2012) Relationships between impulse oscillometry, spirometry and dyspnoea in COPD. *J R Coll Physicians Edinb* 42(2):111–115
- Crim C, Celli B, Edwards LD et al (2011) Respiratory system impedance with impulse oscillometry in healthy and COPD subjects: ECLIPSE baseline results. *Respir Med* 105(7):1069–1078
- Cazzola M, MacNee W, Martinez FJ et al (2008) Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 31(2):416–469
- Short PM, Williamson PA, Elder DH, Lipworth SI, Schembri S, Lipworth BJ (2012) The impact of tiotropium on mortality and exacerbations when added to inhaled corticosteroids and long-acting beta-agonist therapy in COPD. *Chest* 141(1):81–86
- Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF (2010) Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil* 91(2):221–225
- Puhan MA, Chandra D, Mosenifar Z et al (2011) The minimal important difference of exercise tests in severe COPD. *Eur Respir J* 37(4):784–790
- Witek TJ Jr, Mahler DA (2003) Minimal important difference of the transition dyspnoea index in a multinational clinical trial. *Eur Respir J* 21(2):267–272